

What is claimed is:

1. A method to identify compounds useful in regulating insulin resistance in obesity and type II diabetes, comprising:
  - a. administering a compound having melanocyte stimulating hormone (MSH) biological activity to a genetically modified non-human animal comprising a genetic modification within two alleles of its *Pomc* locus, wherein said genetic modification results in an absence of proopiomelanocortin (*Pomc*) peptide activity in said animal, and wherein administration of said compound having MSH activity induces insulin resistance in said animal;
  - b. administering a compound to be evaluated to said non-human animal model; and,
  - c. selecting compounds from (b) that decrease the insulin resistance in said non-human animal as compared to in the absence of said compound of (b).
2. The method of Claim 1, wherein said genetic modification is selected from the group consisting of a deletion, an insertion, a substitution and an inversion of nucleotides in said *Pomc* locus.
3. The method of Claim 1, wherein said genetic modification is a deletion of a nucleic acid sequence within two alleles of said *Pomc* locus, wherein said deletion results in an absence of expression of *Pomc* peptides by said animal.
4. The method of Claim 1, wherein said genetic modification is a deletion of a nucleic acid sequence comprising exon 3 of *Pomc* or a portion of exon 3 of *Pomc* sufficient to prevent expression of *Pomc* peptides by two alleles of the *Pomc* locus.
5. The method of Claim 1, wherein said animal is a mouse, and wherein said genetic modification is a deletion from said genome of exon 3 of *Pomc* (SEQ ID NO:7).
6. The method of Claim 1, wherein said compound having MSH biological activity is selected from the group consisting of: MSH, a biologically active fragment of MSH, a homologue of MSH, a peptide mimetic of MSH, a non-peptide mimetic of MSH, and a fusion protein comprising an MSH protein or fragment thereof.

7. The method of Claim 1, wherein said compound of (a) having MSH biological activity is  $\alpha$ -MSH.

8. The method of Claim 1, wherein said compound of (b) to be evaluated is an antagonist of MSH biological activity.

9. The method of Claim 1, wherein said compound of (b) to be evaluated is administered prior to the step of administering said compound of (a) having MSH biological activity.

10. A method to decrease insulin resistance in a mammal, comprising administering to said mammal that has insulin resistance a therapeutic composition comprising an antagonist of melanocortin stimulating hormone (MSH) biological activity, wherein said antagonist decreases insulin resistance in said mammal.

11. The method of Claim 10, wherein said antagonist of melanocortin stimulating hormone (MSH) is selected from the group consisting of a fragment of MSH having MSH antagonist action, a homologue of MSH having MSH antagonist action, a peptide mimetic of MSH having MSH antagonist action, a non-peptide mimetic of MSH having MSH antagonist action, and a fusion protein comprising any of said MSH antagonist compounds.

12. The method of Claim 10, wherein said antagonist of MSH is a soluble MSH receptor or fragment thereof that binds MSH.

13. The method of Claim 10, wherein said antagonist of MSH is an antibody that selectively binds to MSH and thereby reduces or blocks the activity of MSH.

14. The method of Claim 10, wherein said antagonist of MSH is an antibody that selectively binds to a receptor for MSH and reduces or blocks the ability of MSH to bind to said receptor.

15. The method of Claim 10, wherein said therapeutic composition is administered transdermally.

16. The method of Claim 10, wherein said therapeutic composition is administered topically.

17. The method of Claim 10, wherein said therapeutic composition is administered parenterally.

18. The method of Claim 10, wherein said therapeutic composition is administered in a controlled release formulation.

19. The method of Claim 10, wherein said antagonist of melanocortin stimulating hormone biological activity is administered in a dose of from about 0.1  $\mu$ g to about 10 mg per kg body weight of said animal.

20. A method to treat diabetes associated with insulin resistance in a mammal, comprising administering to said mammal that has insulin resistance and diabetes a therapeutic composition comprising an antagonist of melanocortin stimulating hormone (MSH) biological activity, wherein said antagonist decreases insulin resistance in said mammal.